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Effects of Exercise Training on Cytokines and Adipokines in Multiple Sclerosis: A Systematic Review

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HIGHLIGHTS

- Only 12 studies were found of which 10 studies focused on cytokines, 1 study focused on adipokines, and 1 study included both cytokines and adipokines.
- There is no strong evidence that confirms a positive or negative effect of exercise on cytokine or adipokine in MS patients, yet this research is plagued by methodological weaknesses.
- In relation to cytokines or adipokines, no studies reported harmful effects of exercise
- Regular physical activity did not lead to an increase in pro-inflammatory cytokines or adipokines as well as disease severity.

Effects of Exercise Training on Cytokines and Adipokines in Multiple Sclerosis: A Systematic Review

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Running head: Cytokine and Adipokine in Multiple Sclerosis

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Abstract

Background: Physical activity, particularly exercise training, is an evidence-based approach for managing symptoms, restoring function and improving overall wellness in people with multiple sclerosis (MS). Several recent studies have

argued for a potential disease modifying effect of exercise in people with MS, and among the potential mediating mechanisms are exercise training effects on both cytokines and adipokines. The objectives of this study were to perform a systematic review of exercise training effects on cytokine and adipokine profiles in persons with MS.

Methods: We conducted open-dated searches of PubMed, Cochrane Library, EMBASE and PEDro using the terms 'Multiple sclerosis' or 'MS' AND 'exercise' OR 'training' OR 'physical activity' AND 'cytokine' OR 'inflammatory' OR 'immune' OR 'adipokine'. Included studies were written in English; comprised of humans with MS, and evaluated the effects of regular physical activity or exercise on pro-inflammatory, anti-inflammatory cytokines or adipokines. Two authors independently scanned titles and abstracts, and read the studies included. All studies were rated on the PEDro scale and further classified based on American Academy of Neurology criteria.

Results: Twelve studies were included of which 10 studies focused on cytokines, 1 study focused on adipokines, and 1 study included both cytokines and adipokines. The selected studies included 3 Class I studies, 7 Class II studies, and 2 Class IV studies and had average PEDro scores of 6.9 ± 1.6 . Studies included endurance (n=5), resistance (n=3), combined (n=3), and vibration (n=1) training. Overall, there is a general lack of standardization of procedures across studies and inconsistent evidence for the effects of physical activity and exercise on cytokine and adipokine profiles in MS, with a general pattern indicating a lack of effect.

Conclusion: Research regarding the effects of exercise training on cytokines and adipokines in MS is in its infancy, but exercise represents an adjuvant therapy in MS, and future studies are essential for clarifying the role of exercise on cytokines and adipokines in MS.

Key words: Exercise; Multiple sclerosis; Cytokine; Adipokine; Demyelination

Abbreviations

MS = Multiple sclerosis

Th = T helper

IL = Interleukin

TNF- α = Tumor Necrosis Factor alpha

CNS: Central Nervous System

MeSH: Medical Subject Headings

RCT = Randomized control Trial

PEDro = Physiotherapy Evidence Database

AAN = American Academy of Neurology

RRMS = Relapsing-Remitting Multiple Sclerosis

IFN- γ = Interferon gamma

Vo₂max = maximum Rate of Oxygen

Vo₂peak = Peak rate of Oxygen

1RM = One-repetition Maximum

EDSS = Expanded Disability Status Scale

MVC = Maximum Voluntary Contraction

BDNF = Brain-Derived Neurotrophic Factor

NGF = Nerve Growth Factor

CRP = C-Reaction Protein

TGF- β = Transforming growth factor beta.

1. Introduction

There is increasing emphasis on the importance of regular physical activity, particularly exercise training, among people with multiple sclerosis (MS). The evidence base has resulted in recommendations that exercise training can be incorporated in the comprehensive care of persons with MS for managing many health and wellness aspects of this disease (Herring et al., 2017; Latimer-Cheung et al., 2013; Motl and Pilutti, 2012; Platta et al., 2016). There is further speculation that exercise training may have disease modifying effects for persons with MS (Motl and Pilutti, 2012; Zimmer et al., 2017), and this is largely based on initial evidence for exercise training effects on relapses, brain atrophy and disability progression. Researchers recently suggested a renewed focus regarding the effects of exercise training on cytokines and adipokines based, in part, on the potential for MS disease modification (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Briken et al., 2016; Kjølhed et al., 2016; Mokhtarzade et al., 2017). This renewed focus is further based on evidence for exercise training effects on markers of immune system function in the general populations of adults (Gjevestad et al., 2015; Gondim et al., 2015).

Cytokines are an essential part of the pathophysiology of MS (Patel and White, 2013). Cytokines are proteins secreted from different tissues and influence the reproduction, differentiation, proliferation and function of immune cells (Alexander, 2002). There is a balance between T helper cytokines in healthy persons, whereas in MS this balance shifts and reflects increased Th1 pro-inflammatory cytokines resulting in increases in cytokines such as interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF- α). On the other hand, secretion of Th2 anti-inflammatory cytokines, such as IL-10, is decreased in MS and this can intensify the destruction of myelin and prevent remyelination (Turner et al., 2009). The higher concentration of most pro-inflammatory cytokines is associated with CNS inflammation that is observed in MS pathogenesis and can intensify demyelination processes in the CNS (Lovett-Racke et al., 2004; Patel and White, 2013). Consequently, regulation of the balance between Th1 and Th2 cytokines, and the reduction of inflammation, is accompanied with the control and improvement of MS pathogenic processes involving axonal demyelination and transection (Cannella and Raine, 2004; Lovett-Racke et al., 2004; Sospedra and Martin, 2005; Turner et al., 2009).

The induction of inflammation by the immune system is linked with many factors. One of these factors is adipose tissue and associated cytokine production by adipokines (Ebrahimi et al., 2015; Mokhtarzade et al., 2017), and there is strong evidence that adipokines are involved in the immune pathophysiology of MS (Kraszula et al., 2012; Procaccini et al., 2017; Rotondi et al., 2013). For instance, leptin (as one adipokine) is involved in neurodegenerative and inflammatory processes associated with MS (Rotondi et al., 2013). Previously, studies have verified the role of adipokines on body energy balance and regulation of food intake and body weight, and the important role of leptin in the immunological function via regulation of Th1/Th2 balance are well known (Farrokhi et al., 2016). Cytokines and adipokines closely interact with each other in the immune pathophysiology of MS, and this underscores the importance of monitoring both cytokines and adipokines especially in the immune system of MS.

Disease modifying drugs represent the first line of treatment for MS. These drugs, however, do not provide complete control over the cytokine or adipokine profiles in MS (Mokhtarzade et al., 2017; Motl et al., 2017). This is important as it highlights the important consideration of other approaches for managing the balance of cytokines or adipokines in MS, including exercise training. Indeed, we are aware of three papers that have advocated exercise as a possible disease modifying therapy in MS (Dalgas and Stenager, 2012; Heesen et al., 2006; Majdinasab et al., 2018; Motl et al., 2015) and noted that this may occur through modification of the immune system in persons with MS.

Several mechanisms may mediate the effect of exercise on cytokines, most of which involve the reduction in fat mass subsequently decreasing adipokine secretion and induction of an anti-inflammatory environment through releasing cytokines from contracting skeletal muscle and reduction expression of Toll-like receptors (TLR) on monocytes and macrophages (Gleeson et al., 2011). In general, the concept that exercise independently of weight loss or other interventions can affect cytokines and adipokines is well accepted. Furthermore, there is comprehensive evidence on the role of exercise and physical activity as an anti-inflammatory intervention for modulating cytokines in non-MS subjects (Gleeson et al., 2011; Smart and Steele, 2011). For instance, previous systematic review (Smart and Steele, 2011) that investigated acute and chronic effect of exercise on inflammatory markers such as cytokines in people with a chronic inflammatory disease reported that levels of

inflammatory markers, such as IL-6 acutely increased after exercise and remained elevated longer into the recovery period; Moreover, chronic endurance training can reduce systemic inflammation, especially pro-inflammatory cytokines, in people with type II diabetes and chronic heart failure.

To date, there is no comprehensive systematic review regarding the effect of regular physical activity on cytokine and adipokine expression in MS. We systematically reviewed human randomized control trials (RCTs) and non-RCTs (i.e., clinical trials without a control condition) published before October 2017 that included persons with MS, and examined the effect of exercise training on cytokines and adipokines and provided guidance on future research in this largely neglected area of the biochemical mechanisms that may explain exercise effects in MS.

2. Materials and methods

This review is based on a systematic literature search of 4 electronic databases (PubMed, Cochrane Library, EMBASE, and PEDro) to identify studies that investigated the effect of regular physical activity on cytokines and adipokines in MS, published until October 2017. Physical activity was defined as bodily movement produced by muscle activity that requires more energy than resting, whereas exercise is a subset of physical activity that is planned, structured, and repetitive and has an objective of improving or maintaining physical fitness (Caspersen et al., 1985) (See Box1).

The Medical Subject Heading (MeSH) terms guiding the search included ('Multiple sclerosis' or 'MS') AND ('exercise' OR 'training' OR 'physical activity') AND ('cytokine' OR 'inflammatory' OR 'immune' OR 'Adipokine'). This search strategy identified 142 published articles (Figure 1). Two reviewers independently screened each article based on titles, keywords and abstracts to ensure all articles were captured. Inclusion criteria were: English language, access to full texts, studying the effects of regular physical activity in MS patients (RCT or other clinical trial), studying pro-inflammatory and anti-inflammatory cytokines or adipokines. If a study used other interventions such as medicines or supplements in addition to physical activity, we excluded them from this review. After the omission of duplicate studies,

12 studies were included in the review. Studies included and excluded were reviewed separately by two researchers. The reviewed papers were then examined based on methodological quality and classified based on individual levels of evidence.

2.1. Methodological quality

Methodological quality of studies was evaluated using the original 11-item Physiotherapy Evidence Database (PEDro) scale, which is described in detail elsewhere (Maher et al., 2003). The PEDro scale (Pilutti et al., 2014; Sá, 2014) characterizes the methodological quality of a study based on 11 criteria and yields a score between 0 to 10 (criteria 1 does not add to the score), whereby higher scores indicate superior methodological quality. Scores between 0-4 reflect low methodological quality, scores between 5 or 6 reflect fair methodological quality, and scores between 7-10 reflect high methodological quality (Foley et al., 2003) (for more information https://www.pedro.org.au/wp-content/uploads/PEDro_scale.pdf).

2.2. Classification and recommendations

Classification of studies was carried out according to the criteria provided by the American Academy of neurology (ANN). ANN classification is a standard published index for therapeutic studies that divides studies into four levels of evidence (supplement data table 1). After classification of reviewed studies, overall recommendations (based on ANN guidelines) were provided based on physical activity/exercise having a positive, neutral, or harmful effect on cytokines and adipokines within the four recommend Classes (see supplement data table 2) (Sandroff et al., 2016).

3. Results

3.1. Study characteristics

We located 907 studies, and 12 articles were eligible to be included in this review after examining inclusion and exclusion criteria. Ten studies focused on the effect of exercise training on cytokines, one study focused on the effect of exercise training on adipokines, and one study included both cytokines and adipokines as outcome measures (Mokhtarzade et al., 2017). The characteristics of the 12 studies regarding clinical characteristics and exercise protocol are reported in Table 2. There were 412 participants included in the reviewed studies; 22 of them were healthy controls and 366 of them were individuals with MS. Regarding gender, 261 (71%) participants were women, and the remainder were male ($n=105$, 29%). Two studies included only women (Golzari et al., 2010; Mokhtarzade et al., 2017), whereas both genders were included in 10 studies (83%) (Alvarenga-Filho et al., 2016; Briken et al., 2016; Castellano et al., 2008; Deckx et al., 2016; Ebrahimi et al., 2015; Kierkegaard et al., 2016; Kjølhed et al., 2016; Schulz et al., 2004; White et al., 2006). Among the 46 subjects who dropped-out of the studies, 32 cases were in the exercise training groups (14%) and 14 cases were in the control groups (9%). There were 2 (1%) and 5 (3%) cases excluded from both the training and control groups, respectively, based on the occurrence of a relapse. Participant age was between 18 and 60 years. Seven studies focused on RRMS type of MS (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Ebrahimi et al., 2015; Kierkegaard et al., 2016; Kjølhed et al., 2016; Mokhtarzade et al., 2017; White et al., 2006), whereas 2 studies included two types of MS (Deckx et al., 2016; Mokhtarzade et al., 2017) or did not report the type of MS (3 studies: 25%). MS diagnosis in 4 studies (Bansi et al., 2013; Deckx et al., 2016; Ebrahimi et al., 2015; Kjølhed et al., 2016) was based on McDonald (McDonald et al., 2001) or revised McDonald (Polman et al., 2011) criteria; 2 studies (Castellano et al., 2008; Schulz et al., 2004) used Poser (Poser et al., 1983) criteria, whereas the other studies did not specify diagnostic criteria or use any other criteria for MS diagnosis. EDSS scores of MS subjects in these studies were between 0 and 6.5. All studies except Kierkegaard et al., 2016 and White et al., 2006 had two group comparisons (training vs. control group). Bansi et al., 2013 compared land versus water-based exercise. Alvarenga-Filho et al., 2016 was the only study to use a healthy matched control group as well as trained and untrained MS groups (see studies description in supplement materials)

The reviewed studies used aerobic or endurance (5 studies), resistance (3 studies), combined (3 studies) and vibration (1 study) training (see table 2), but no studies had the same exercise training protocol. The frequency of exercise sessions was 2 or 3 sessions per week in the studies. Most studies did not report any progression in the session's frequency during the training period. Intensity of exercise was moderate and high in most studies, and was designed based on heart rate,

maximum watts and maximal aerobic capacity. Exercise intensity was considered constant, and the applied progression of exercise intensity was not reported. The duration of the training protocol ranged between 3 (Bansi et al., 2013) and 24 (Kjølhede et al., 2016) weeks.

IL-6 and TNF- α were the most commonly assayed cytokines with IL-6 reported in 8 studies (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Briken et al., 2016; Castellano et al., 2008; Deckx et al., 2016; Kierkegaard et al., 2016; Schulz et al., 2004; White et al., 2006) and TNF- α in 7 studies (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Castellano et al., 2008; Deckx et al., 2016; Kjølhede et al., 2016; Mokhtarzade et al., 2017; White et al., 2006). IL-10 (Alvarenga-Filho et al., 2016; Deckx et al., 2016; Kjølhede et al., 2016; Mokhtarzade et al., 2017; White et al., 2006) and IFN- γ (Alvarenga-Filho et al., 2016; Castellano et al., 2008; Golzari et al., 2010; Kjølhede et al., 2016; White et al., 2006) were both included in 5 studies. Leptin was the most commonly reported adipokine in the reviewed studies (2 studies, see table 3).

3.2. Methodological quality and study classification

The PEDro scale described the methodological quality of studies. PEDro scores ranged between 3 and 8, and the mean PEDro scale score was 5.9 ± 1.5 , reflecting fair methodological quality (table 1). Five studies (Briken et al., 2016; Deckx et al., 2016; Kjølhede et al., 2016; Mokhtarzade et al., 2017; Schulz et al., 2004) were of high quality (score 7 and above). Of the 12 studies included in the current review, 3 provided Class I evidence, 7 Class II evidence, and 2 Class IV evidence; there were no studies providing Class III evidence.

3.3. Classification of Evidence

3.3.1. Cytokines

Evidence from 7 of 8 studies (i.e., 1 Class I study and 6 Class II studies,) does not support the efficacy of exercise training for changing IL-6 concentration due to non-significant results (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Briken et al., 2016; Castellano et al., 2008; Deckx et al., 2016; Schulz et al., 2004; White et al., 2006), however one study (Kierkegaard et al., 2016) did report a reduction. Therefore, current data on IL-6 resulted in classification B.

Evidence from 4 of 7 studies focused on TNF- α included 1 Class I study (Kjølhed et al., 2016) and 3 Class II studies (Alvarenga-Filho et al., 2016; Bansi et al., 2013; White et al., 2006), does not support the efficacy of regular exercise training. Evidence from 1 of 7 studies (Class II) does support the efficacy of exercise training for significantly increasing TNF- α levels (Castellano et al., 2008), while 2 studies including Class I (Mokhtarzade et al., 2017) and Class II (Deckx et al., 2016) report reduction of TNF- α level in an individual with MS. Therefore, current results classify as non-applicable, since data sets are inadequate and conflicting.

The results of 4 of 5 studies (2 Class I and 2 Class II) do not support the efficacy of exercise training for improving IL-10 level based on non-statistically significant results (Alvarenga-Filho et al., 2016; Deckx et al., 2016; Kjølhed et al., 2016; Mokhtarzade et al., 2017). Moreover, 1 of 5 studies (Class IV) indicate efficacy of exercise training to decrease IL-10 level in MS subjects (White et al., 2006). Taken together, this resulted in classification A, since exercise training is ineffective in changing IL-10 levels in persons with MS.

Evidence and results from other cytokine studies are not meaningful and do not support the efficacy of exercise training for improving the cytokine profile. Therefore, results from other cytokines are classified as non-applicable based on conflicting evidence, in the sense that data are inadequate or conflicted.

3.3.2. Adipokines

Only 2 studies investigated effect of exercise training on adipokines in people with MS. One of the 2 studies provided Class I evidence and indicated an effect of exercise training for improving leptin (Mokhtarzade et al., 2017), yet 1 Class II study (Ebrahimi et al., 2015) indicated that exercise training did not have an effect on leptin. Therefore, current evidence is described as non-applicable reflecting that the data are inadequate or conflicting.

4. Discussion

There is a small corpus of research examining the effect of regular physical activity on the pathophysiology of MS with an emphasis on cytokines or adipokines. The present systematic review included 12 studies on the effects of exercise training on cytokine and adipokine profiles in persons with MS. This included 3 Class I studies, 7 Class II studies, and 2 Class IV studies on cytokines, and only 1 Class I study and 1 Class II study on adipokines. Overall, most studies do not support a substantial impact of exercise training on cytokines and adipokines in persons with MS, but methodological flaws of the studies may bias a clear interpretation. However, no harmful effects of exercise modalities were noted for cytokines or adipokines, although this was not the intended purpose of the studies and the studies did not examine exercise effects during a relapse.

4.1. Effect of exercise on Cytokines

The cytokines that are of primary focus in MS studies include a diverse spectrum of pro-inflammatory cytokines such as IL-1, IL-2, IL-6, IL-17, IFN- γ and TNF- α , and anti-inflammatory cytokines such as IL-1ra, IL-4 and IL-10. The major source of most of these cytokines are immune system cells such as T cells, macrophages, B cells, monocytes and natural killer cells that can induce inflammatory or anti-inflammatory effects through different mechanisms (Kierkegaard et al., 2016; Kjølhed et al., 2016).

Though significant work has been done in the study of the cytokine changes with exercise in the general population (Gjevestad et al., 2015; Gondim et al., 2015), the effect of exercise on cytokines remains inconclusive in MS subjects. For example, two Class IV studies (Kierkegaard et al., 2016; White et al., 2006) reported significant decreases in the level of IL-4 after training, whereas one Class I (plasma level) and one Class II (plasma level and production by peripheral blood mononuclear cell, PBMC) study (Golzari et al., 2010; Kjølhed et al., 2016) did not find any differences. This contradiction in results was observable in other cytokines,

and makes it difficult to surmise a definitive conclusion on the effects of regular physical activity in MS subjects; although there is no doubt about the usefulness of regular physical activity for MS patients particularly for improved fitness and corresponding quality of life (Herring et al., 2017; Sandroff et al., 2016).

Among the reviewed studies, 5 studies investigated the effect of regular physical activity on IL-10. Four studies (two Class I and two Class II studies) reported no change for IL-10 level (Alvarenga-Filho et al., 2016; Deckx et al., 2016; Kjølhed et al., 2016; Mokhtarzade et al., 2017) and one Class IV study reported a significant reduction (White et al., 2006). IL-10, known as human cytokine synthesis inhibitory factor, is an anti-inflammatory cytokine associated with MS relapses. It should be noted that Alvarenga-Filho et al., 2016 and Deckx et al., 2016 elevated IL-10 secretion from T cells and regulatory type 1 cells, respectively, which was different with other studies that elevated IL-10 levels in serum and plasma. Evidence suggests that IL-10 secreted by Th2 cells down-regulates the production of pro-inflammatory cytokines from Th1 cells (Mokhtarzade et al., 2017). Moreover, IL-10 is an important factor for monitoring the response to medication and disease progression. Specifically, treatment with IFN- β increases concentrations of IL-10 to protect against the pro-inflammatory cytokines such as IFN- γ and TNF- α (Mokhtarzade et al., 2017). Therefore, increase in the level of IL-10 could partly explain the beneficial effect of regular physical activity in MS subjects. However, most of the reviewed studies report no marked change on IL-10 anti-inflammatory factor.

It seems that IL-10 is affected by multiple factors, such as adiposity, baseline fitness and exercise duration (Alvarenga-Filho et al., 2016; Briken et al., 2016; Mokhtarzade et al., 2017). So, short training periods (often less than 8 weeks) and the low level of the physical fitness of MS patients compared to healthy individuals are two major reasons for the inefficiency of regular physical activity on cytokines in the reviewed studies (Briken et al., 2016; Kjølhed et al., 2016; Mokhtarzade et al., 2017). On the other hand, most of reviewed studies have not paid attention to the metabolic and/or body composition changes resulting from training that can affect the immune system and its adaptation to exercise. Interestingly, Mokhtarzade et al., 2017 demonstrated that IL-10 changes following interval aerobic exercise training is associated with improved aerobic capacity in MS subjects. Mokhtarzade et al., 2017 concluded that the low level of physical fitness in MS subjects is probably one of the reasons for the lack of significant improvement in IL-10 level after a training period. In addition, Weinhold et al., 2015 reported that increasing levels of IL-10,

which is produced from the regulatory T-cells, after exercise is associated with fitness level (Weinhold et al., 2016). It is worth noting that investigating the role of anti-inflammatory cytokines in the context of MS regardless of pro-inflammatory cytokines such as IL-6 and TNF- α can be incomplete.

One Class I, five Class II and two Class IV studies focused on the effect of regular physical activity on IL-6, from which one Class IV study reported a significant reduction (Kierkegaard et al., 2016) and other studies have reported no considerable change (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Briken et al., 2016; Castellano et al., 2008; Deckx et al., 2016; Schulz et al., 2004; White et al., 2006) after a training period. Similar to IL-10, IL-6 results are also contradictory; however most of the studies show that the serum level of IL-6 is not changed after the training. One common theme across studies is that the overall unconvincing evidence for IL-6 might be biased by studies that did not assess IL-6 in several tissues such as muscle and adipose, and also failure to report the pharmacological treatment effect on cytokine status. Interestingly, one Class II study (Alvarenga-Filho et al., 2016) indicated that serum levels of IL-6 is chronically higher in MS subjects and there is a significant relationship between IL-6 and fatigue. Despite this, in our laboratory and in an unpublished study, we observed that the level of IL-6 is higher in relapse and remitting MS subjects at rest. Furthermore, IL-6 exacerbates the demyelination process and inflammation (Sharief, 1998). Based on the importance of IL-6 in the CNS, reduction of this factor is of potential great clinical significance in MS patients (Sharief, 1998). Based on the stimulating effects on T cells and the data suggesting that IL-6 has the potential to aid in the progression of MS (Arnett et al., 2003; Molanori Shamsi, 2010), many studies have considered IL-6 as a pro-inflammatory cytokine, but some studies emphasize the anti-inflammatory role of IL-6 (Alvarenga-Filho et al., 2016; White et al., 2006). IL-6 secretion from skeletal muscle during exercise stimulates hepatic glucose release into the circulation. The reduced resting concentrations of IL-6 after adaptation to exercise in healthy and obese subjects was associated with a reduction in glucose dependence (Agha Alinejad et al., 2010; Molanori Shamsi, 2010; Ozenci et al., 1999).

Another important and interesting pro-inflammatory cytokine is TNF- α . Seven studies investigated the effect of exercise training on TNF- α , and these studies include one Class I, three Class II and one Class IV study have reported no significant change (Alvarenga-Filho et al., 2016; Bansi et al., 2013; Deckx et al., 2016; Kjølhede et al., 2016; White et al., 2006). Only one Class II (Golzari et al., 2010) and one Class I (Mokhtarzade et al., 2017) study showed significant increases and decreases in TNF- α levels, respectively. Overall, the evidence for the effects of exercise training on TNF- α was conflicting, and involved studies of relatively weak

methodological quality (i.e., only 1 Class I study). However, the contradictory results may result from a dual role of TNF- α . Although, it has been reported that an increase in TNF- α is associated with disturbance of the blood brain barrier and axonal demyelination (Elenkov and Chrousos, 2002; Minagar and Alexander, 2003), TNF- α is also associated with the reduction in the relapse events with IFN- β treatment (Sharief and Hentges, 1991; Simpson et al., 2015) and stimulation of remyelination by increasing the oligodendrocyte proliferation (Arnett et al., 2003).

The dual role of TNF- α in MS disease is complex. Reports suggest that exercise training increases the p75 receptor protein concentrations promoting neuroprotection (Mokhtarzade et al., 2017). It should also be noted that in damaged cells and in cancer pathology, the pathway of both TNF- α receptors is associated with cell death and induction of inflammation (Arnett et al., 2001; Arnett et al., 2003; Elenkov and Chrousos, 2002); a plausible response in the cells of the CNS during MS relapses and progression. As stated, one of the human pro-inflammatory cytokine synthesis inhibitory factors is IL-10, but almost all studies suggest that exercise cannot improve IL-10 secretion. Therefore, the non-reduction in TNF- α response to training in previous studies, can be attributed to the lack of change in IL-10.

4.2. *Effect of exercise on adipokines*

Two studies evaluated the effect of regular physical activity on the peripheral blood circulation level of adipokines. In these studies, vibration and interval aerobic exercises were used as interventions, and the studies observed either no change or a decrease in the resting levels of leptin, as an inflammatory mediator. A Class II study (Ebrahimi et al., 2015) observed no change in leptin as an inflammatory mediator, Ghrelin or body mass index. The relationship between leptin and fat mass, and the lack of significant change in fat mass may help explain this result. This study had some methodological concerns from an exercise prescription standpoint. Indeed, it seems that vibration training was not intense enough; therefore, the maximal benefits of exercise training on leptin could not be realized. On the other hand, the Class I study (Mokhtarzade et al., 2017) reported a significant decrease in serum levels of leptin and a significant increase in adiponectin. The results also showed a significant improvement in the body composition profile of MS subjects.

Recent studies have focused on the role of adipose tissue and secreted adipocytokines from adipose tissue such as leptin (Devorak et al., 2017; Frisullo et al., 2004; Kraszula et al., 2012; Meier and Gressner, 2004; Procaccini et al., 2017). Evidence has supported important and complex features of the interaction between nutrition, metabolism and the hemostasis of the immune system (Procaccini et al., 2017; Procaccini et al., 2015). Therefore, leptin is considered a pivotal factor to control weight by controlling nutrition and consumption of energy. It has also been suggested that leptin plays an important role in the regulation of several adaptive and innate immune functions (Procaccini et al., 2017). In other words, leptin plays a key role in connecting metabolic changes and the immune system. In fact, leptin stimulates T cell proliferation, monocyte and macrophage activity and production of inflammatory cytokines (IL-1, IL-12 and TNF- α) (Kraszula et al., 2012; Meier and Gressner, 2004; Procaccini et al., 2015). Frizullo et al., 2004 have demonstrated that leptin is related to the relapse of MS by stimulating the secretion of IL-6 and TNF- α . Consequently, interpretation of leptin's role based on cytokine changes can provide interesting conclusions.

4.3. Future research

There is a complex link between the immune system and adipose tissue. On the other hand, adipose tissue is associated with other risks, including cardiovascular risk and even mortality (Hedström et al., 2012; Lin et al., 2017; Munger et al., 2013). With leptin as an example, the three-way connection between nutrition, metabolism and the immune system needs to be examined. Recent research has reported that, in addition to leptin, other adipocytokines, such as adiponectin and resistin, may affect the immune system (Kraszula et al., 2012) and may have role in MS pathogenesis, requiring further research. One of the main causes of difference in the results reviewed in this paper are likely attributable to differences in exercise protocol type, duration and exercise intensity. Reviewed studies have often used only a single type of exercise as an intervention, and there is no comparison between different types of exercise and intensities. Therefore, it is suggested that comparisons between different exercises should be made to determine the most effective exercise modality in terms of the effect on cytokine profile. Furthermore, there are significant requirements for standardized high quality studies that investigate both short and long term effects of an active lifestyle on clinical and Para clinical parameters in patients with MS. Although most studies did not show chronic effects of exercise on cytokines, we know that acute effects may also be important. It may

be that the positive effects of exercise should rather be seen as the sum of acute effects, leading to long term improvements (Bansi et al., 2013; Kjølhed et al., 2016). It seems that acute exercise induces a short term inflammatory environment, this is followed by a mid-term anti-inflammatory environment; therefore, studies should particularly pay attention to the acute effects of exercise and the role of an exercise training program on the acute response of cytokines to exercise.

One of the most important mechanisms that may play a decisive role in exercise effect on cytokines is weight loss during exercise program (Gleeson et al., 2011). This has not been taken into consideration in most studies of exercise training in MS. It has been reported in Mokhtarzade et al., 2017 that weight loss following exercise is associated with an increase in the level of anti-inflammatory cytokines such as IL-10 and Adiponectin in pwMS. Therefore, in future studies, special attention should be paid to the concept of weight loss and its role in the effect of exercise on cytokines and adipokines in MS.

Future research needs to incorporate as many of these quality measures to ensure accurate and reliable results are obtained with respect to MS disease. Moreover, other methodological weakness across the reviewed studies include the absence of healthy controls, engaged in similar training programs to compare directly the pattern of adaptability of healthy people with those individuals with MS. Although, studies that have been conducted on healthy subjects or even other diseases, suggest a positive and modulating effect on exercise training on cytokines and adipokines. Finally, there is an obvious gap in our understanding of the additive or synergistic role of pharmaceutical therapies and exercise that are important for guiding future research.

4.4. Limitations

One of the limitations of this study is that the results may not be generalizable to all MS patients; because the majority of studies recruited small samples of MS patients. On the other hand, most studies have not explained how to determine their sample sizes. Therefore, studies may suffer from type II statistical errors (incorrect rejection of a true null hypothesis). In addition, some studies (Golzari et al., 2010; Mokhtarzade et al., 2017) have only used females as samples, while the male to female ratio is 2 to 1 in MS, making generalizing the results difficult to all MS patients. However, Mokhtarzade et al., 2017 finds that males and females have different adipokines adaptation to the training period, and a different adipokine background between male and female subjects can result in an experimental bias (Mokhtarzade et

al., 2017). Other limitations of reviewed studies is the heterogeneity of the MS population study; some studies focused on RRMS patients but some studies focused or used other type of MS which maybe have major differences in the pattern of response of adipokines and cytokines.

Based on the investigation effect of exercise training on a wide range of cytokines and adipokines, lack of consistent reporting and heterogeneity of experimental design and varied type of exercise programs used in the reviewed studies, performing a meta-analysis was not possible. Moreover, in two studies the dropout exceeded 15% and the main outcome measure was obtained from less than 85% of the sample (Deckx et al., 2016; Kierkegaard et al., 2016) this may result in insufficient power to detect statistically significant changes.

Cytokines can be monitored using a variety of tools, methods and in different sites. Most studies have focused on assessing cytokines in serum, while assaying cytokines in the serum have several problems and can be inaccurate. Therefore, methods used to measure cytokines can be consider as a major limitations of the existing studies which can lead to the heterogeneity of results.

A further limitation is related to database that were used in the current review study. Only articles published in 4 databases (PubMed, Cochrane Library, EMBASE, and PEDro), and English peer-reviewed journals, were included in the current study. Therefore, this review may have not been comprehensive enough to include all studies on the effects of exercise training on cytokines and adipokines profiles in MS patients. Despite this, databases used in the current review study are major electronic databases that index a great number of studies. In addition, the class of reviewed studies is limited, for example, cross over-design or cohort studies are necessary, and could make the conclusions of this study stronger.

The majority of studies have neglected important notes in their methodology. For instance, nutritional considerations, menstrual cycle in females and the accurate assessment of the body composition were not considered completely. All these factors could influence outcomes, and could help in the interpretation of the effects of exercise training. In other hand, weight loss and body composition changes are one of the most important factors affecting adipokines and cytokines, while most studies have not been monitored body composition and weight loss response to exercise training. Finally, a short-term exercise period of some reviewed studies (three to eight weeks) is another important cause for null effect of exercise training.

4.5. Conclusion

Overall, the limited and contradictory results that are summarized in the current study suggest that more extensive research is needed to better understand and quantify the role of regular physical activity on cytokines and adipokines in MS, while resolving the methodological weaknesses outlined in this study. The lack of systematic changes in cytokines and adipokines indicates that an anti-inflammatory effect of exercise is not the main underlying mechanism that mediates positive effects of exercise on outcomes such as EDSS, fatigue and other clinical outcomes following a short-term training period (less than 6 months) in persons with MS. Importantly, no studies reported any harmful effects of exercise in relation to cytokines or adipokines and regular physical activity did not lead to inflammation or an increase in adipokines or in disease severity. Therefore, these findings indicate that an active lifestyle can be considered as an important part of MS treatment. Finally, evidence does not support the notion that the potential disease modifying effect of exercise in MS should be driven by underlying changes in cytokines

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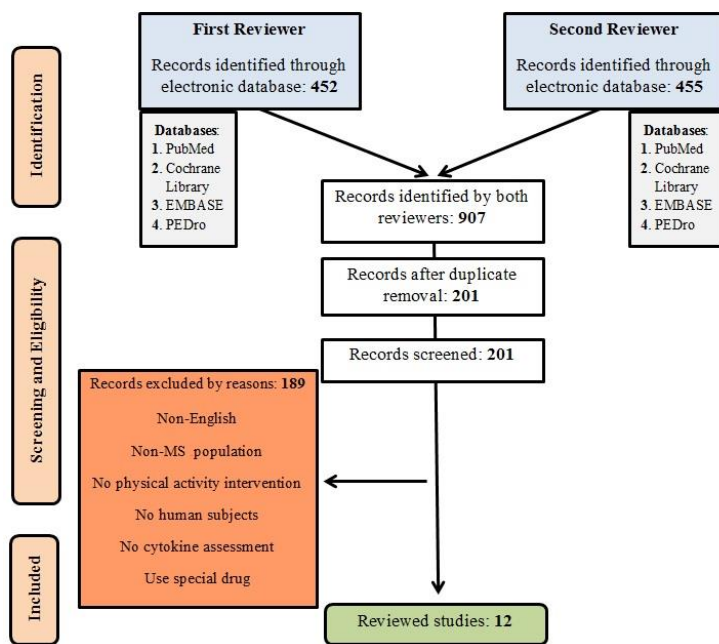


Figure 1 Flowchart of search results and study selection. Inclusion criteria was: English language, enrollment of MS patients, access to full text, studying regular physical activity, studying cytokines.

Table 1 The methodological quality of the reviewed studies using the PEDro scale and ANN classification.

	Scales												ANN classification
First author Year	#1	#2	#3	#4	#5	#6	#7	#8	#9	#10	#11	Total	
Mokhtarzade 2017	1	1	1	1	0	0	0	1	1	1	1	7/10	I
Briken 2016	1	1	1	1	0	0	0	1	1	1	1	7/10	I
Alvarenga-Filho 2016	1	0	0	1	0	0	0	1	1	1	1	5/10	II
Deckx 2016	1	1	1	1	0	0	1	0	1	1	1	7/10	II
Kierkegaard 2016	1	0	0	1	0	0	0	0	1	0	1	3/10	IV
Kjølhede 2015	1	1	1	1	0	0	1	1	1	1	1	8/10	I
Ebrahimi 2015	1	1	0	1	0	0	0	1	1	1	1	6/10	II
Bansi 2012	1	1	0	1	0	0	0	1	1	1	1	6/10	II
Golzari 2010	1	1	0	1	0	0	0	1	1	1	1	6/10	II
Castellano 2008	1	1	0	1	0	0	0	1	1	1	1	6/10	II
White 2006	1	0	0	0	0	0	0	1	1	0	1	3/10	IV
Schulz 2004	1	1	0	1	0	0	1	1	1	1	1	7/10	II

#1: Eligibility criteria (not included in the total score); #2: Random allocation; #3: Allocation was concealed; #4: The groups were similar on important criteria at the baseline; #5: Blind all subjects; #6: Blind therapy administration; #7: Blind all assessors; #8: Outcomes were obtained from more than 85%; #9: Intention to treat analysis; #10: Statistical comparisons between groups at least for one key factor; #11: Point estimates and variability.

Table 2 Characteristics and protocol of the reviewed studies

First author Year	MS type	Subjects	Age (years)	EDSS	Exercise Type	Duration and Intensity
Mokhtarzade 2017	RRMS	Training group: 22	32.0 ± 2.8	1.8 ± 0.4	Aerobic training:	8-week, 3 sessions per
		Control group: 18	31.3 ± 3.3	1.6 ± 0.6	Upper and lower limb cycling	week, 60-75% W _{max}
Briken 2016	PPMS & SPMS	Training group: 28	49.9 ± 7.6	4.9 ± 0.9	Endurance training:	9-week, 2-3 sessions per
		Control group: 9	50.4 ± 7.6	4.9 ± 0.8	arm ergometry, rowing and bicycle ergometry	week
Alvarenga-Filho 2016	RRMS	MS trained: 8	41.1 ± 12.9	0-2	Combined training:	12-week, 3 sessions per
		MS untrained: 10	35.2 ± 7.6	0-2.5	Cycling and Pilates exercises	week
		Healthy control: 10	39.7 ± 10.4			
Deckx 2016	RRMS & CPMS	Training group: 29	47 ± 2#	3 ± 0.2#	Combined training:	12-week, 5 sessions per 2
		Control group: 16	50 ± 3#	3 ± 0.4#	Cycling, walking, running and resistance training	weeks

Kierkegaard 2016^a	RRMS	Training group: 20	36.3±7.6	1-2.4	Whole body resistance training	12-week, 2 sessions per week, 80% 1RM
Kjølhede 2015	RRMS	Training group: 16 Control group: 16	44.6±7 42.2±8	2.9 ± 1 2.9 ± 1	Upper and lower resistance training	24-week, 2 sessions per week
Ebrahimi 2015	RRMS	Training group: 16 Control group: 14	37.1±8.4 40.8±10.6	3.1 ± 1.2 3.1 ± 0.8	Whole body vibration	10 week, 3 sessions per week
Bansi 2012	NR	Land group: 28 Water group: 24	46.7–56.3 44.6–55.1	4.1–5.3 4.0–5.2	Endurance training: Ergometer land and water group	3-week, 70% HR _{peak}
Golzari 2010	NR	Training group: 10 Control group: 10	32.2±7.6 33.8±8.2	2.1±1.1 2.0 ±1.1	Combined training: Endurance and resistance training	8-week, 3 sessions per week
Castellano 2008	RRMS	MS trained: 11 Healthy trained: 11	40±10 40±10	0-5.5	Aerobic cycling training	8-week, 3 sessions per week, 60% V _{O₂peak}
White 2006*	RRMS	Training group: 10	47±12	3.8±0.9	Lower limb resistance training	8-week, 2 sessions per week, 50-70% MVC
Schulz 2004	NR	Training group: 15 Control group: 13	39±9 40±11	2.0±1.4 2.5±0.8	Aerobic cycling training	8-week, 2 sessions per week, 75% W _{max}

* Kierkegaard et al 2016 and White et al 2006 only used one group in their study, # Data Shown SD \pm SEM, NR: not reported; MS: multiple sclerosis; RRMS: relapsing-remitting MS; PPMS: primary progressive MS; SPMS: secondary progressive MS; CPMS: Chronic Progressive MS; EDSS: Expanded Disability Status Scale; W_{max}: watts maximum; 1RM: one repetition maximum; HR_{peak}: peak heart rate; Vo_{2peak}: peak oxygen consumption; MVC: maximum voluntary contraction.

Table 3 The overall results of the reviewed studies

First author Year	Main factors	Sampling time		Sample			Main results
		RE	AE	S	P	C	
Mokhtarzade 2017	IL-10, TNF- α , Leptin, Adiponectin	×		×			Responses to 8 weeks exercise training (cytokines): TNF- α ↓; IL-10 and IL-10/TNF- α ratio underwent no considerably change. Responses to 8 weeks exercise training (Adipokines): leptin ↓, Adiponectin ↑, Leptin/Adiponectin ↓. Clinical outcome: Fatigue ↓, QoL ↑.
Briken 2016	Irsin, BDNF, IL-6	×	×	×			Responses to acute exercise: BDNF ↑ (immediately after exercise); Irsin and IL-6 underwent no considerably change. Responses to 9 weeks exercise training: Irsin, BDNF and IL-6 underwent no considerably change. Clinical outcome: Not reported.

Alvarenga-Filho 2016	IL-6, IL-10, IL-21, IL-22, TNF- α , IFN- γ	×					Responses to 12 weeks exercise training: IL-22 ↓; Other cytokines underwent no considerably change. # Clinical outcome: Fatigue ↓.
Deckx 2016	IL-6, IL-10, IL-12, TNF- α , TGF- β	×			×		Responses to 12 weeks exercise training: All measured cytokines underwent no considerably change. TNF- α secretion ↓ (upon LPS and IFN- γ stimulation). Clinical outcome: Not reported.
Kierkegaard 2016	IL-1ra, IL-4, IL-5, IL-6, IL-7, IL-8, IL-12, IL-13, IL-17	×			×	×	Responses to 12 weeks exercise training: Serum level of all measured cytokines ↓; CSF level of all measured cytokine underwent no considerably change. Clinical outcome: Anxiety ↓, Depression ↓, Fatigue ↓.
Kjølhede 2015	IL-1 β , IL-4, IL-10, IL-17, IL-23, TNF- α , IFN- γ	×	×		×		Responses to acute exercise: All measured cytokine underwent no considerably change in the beginning (untrained state) and after of 24 weeks of exercise training (trained state). Responses to 12 weeks exercise training: All measured cytokines underwent no considerably change. Clinical outcome: Walking ability ↑.
Ebrahimi 2015	Leptin, Gerlin, Testosterone	×		×			Responses to 10 weeks exercise training: Leptin, ghrelin and testosterone levels, ghrelin/leptin and testosterone/leptin ratio underwent no considerably change. Clinical outcome: EDSS ↓, Walking ability ↑, Balance ↑.
Bansi	IL-6, TNF- α ,	×	×		×		Responses to acute exercise: BDNF ↑; IL-6, TNF- α , sIL-6R and NGF underwent no considerably

2012	sIL-6R, BDNF, NGF						change. Responses to 3 weeks exercise training: BDNF ↑ (water group); IL-6, TNF- α , sIL-6R and NGF underwent no considerably change. Clinical outcome: Fatigue showed no considerably change.
Golzari 2010	IL-4, IL-17, IFN- γ	×			×		Responses to 8 weeks exercise training: IL-17 ↓, IFN- γ ↓; IL-4 underwent no considerably change.* Clinical outcome: EDSS ↓, Balance ↑.
Castellano 2008	IL-6, TNF- α , IFN- γ	×	×		×		Responses to acute exercise: 30 min postexercise IL-6 ↑, TNF- α ↓, IFN- γ ↓. Responses to 8 weeks exercise training: TNF- α ↑, IFN- γ ↑; IL-6 underwent no considerably change. Clinical outcome: EDSS ↓.
White 2006	IL-2, IL-4, IL-6, IL-10, IFN- γ , TNF- α , CRP	×		×			Responses to 8 weeks exercise training: IL-4 ↓, IL-10 ↓, CRP ↓, IFN- γ ↓, IL-2 ↓; IL-6 and TNF- α underwent no considerably change. Clinical outcome: Fatigue ↓.
Schulz 2004	IL-6, sIL-6R, BDNF, NGF	×			×		Responses to 8 weeks exercise training: IL-6, sIL-6R, BDNF and NGF underwent no considerably change. Clinical outcome: QoL ↑, Balance ↑.

MS: multiple sclerosis; IL: Interleukin; IL-1ra: interleukin-1 receptor antagonist; sIL-6R: Soluble IL-6 receptor; IFN- γ : Interferon gamma; CRP: C-reactive protein;

BDNF: Brain-derived neurotrophic factor; NGF: Nerve growth factor; TGF- β : Transforming growth factor beta. LPS: Lipopolysaccharides, EDSS: Expanded disability status scale, QoL: Quality of life, RE: rest, AE: after an exercise bout, S: serum, P: plasma or supernatant, C: Cerebrospinal fluid, ↑: significant increase, ↓: significant decrease.

These results are based on cytokines that are produced by T cells.

* These results were measured in both plasma concentrations and production by peripheral blood mononuclear cell (PBMC) status.